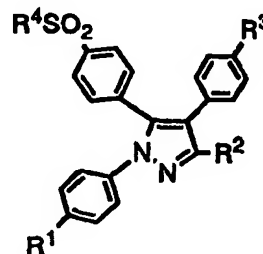




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 231/12, A61K 31/415	A1	(11) International Publication Number: WO 95/15317 (43) International Publication Date: 8 June 1995 (08.06.95)
<p>(21) International Application Number: PCT/US94/12721</p> <p>(22) International Filing Date: 14 November 1994 (14.11.94)</p> <p>(30) Priority Data: 08/161,004 30 November 1993 (30.11.93) US</p> <p>(60) Parent Application or Grant (63) Related by Continuation US 08/161,004 (CIP) Filed on 30 November 1993 (30.11.93)</p> <p>(71) Applicant (for all designated States except US): G.D. SEARLE & CO. [US/US]; Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US).</p> <p>(72) Inventor; and (75) Inventor/Applicant (for US only): LEE, Len, F. [US/US]; 2496 Annapolis Way, St. Charles, MI 63303 (US).</p> <p>(74) Common Representatives: BULOCK, Joseph, W. et al.; G.D. Searle & Co., Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US).</p>	<p>(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ).</p> <p>Published <i>With international search report.</i></p>	
<p>(54) Title: 1,4,5-TRIPHENYL PYRAZOLYL COMPOUNDS FOR THE TREATMENT OF INFLAMMATION AND INFLAMMATION-RELATED DISORDERS</p> <p>(57) Abstract</p> <p>A class of 1,4,5-triphenyl pyrazoles is described for the treatment of inflammation, including treatment of pain and disorders such as arthritis. Compounds of particular interest are of formula (II), wherein R¹ is selected from the group hydrido, halo, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, nitro, amino, N-monoalkylamino, N,N-dialkylamino, acylamino, acylaminoalkyl, haloalkyl, hydroxy and alkoxy; wherein R² is selected from hydrido, alkyl, cyano and haloalkyl; wherein R³ is selected from the group hydrido, halo, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, nitro, amino, N-monoalkylamino, N,N-dialkylamino, acylamino, acylaminoalkyl, haloalkyl, hydroxy and alkoxy; and wherein R⁴ is alkyl or amino; or a pharmaceutically-acceptable salt thereof.</p> <div style="text-align: right;">  <p>(II)</p> </div>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Larvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

1,4,5-TRIPHENYL PYRAZOLYL COMPOUNDS FOR THE
TREATMENT OF INFLAMMATION AND INFLAMMATION-RELATED
DISORDERS

5

FIELD OF THE INVENTION

This invention is in the field of anti-inflammatory pharmaceutical agents and specifically relates to compounds, compositions and methods for treating inflammation and inflammation-associated disorders, such as arthritis.

BACKGROUND OF THE INVENTION

15

Prostaglandins play a major role in the inflammation process and the inhibition of prostaglandin production, especially production of PGG₂, PGH₂ and PGE₂, has been a common target of anti-inflammatory drug discovery. However, common non-steroidal anti-inflammatory drugs (NSAIDs) that are active in reducing the prostaglandin-induced pain and swelling associated with the inflammation process are also active in affecting other prostaglandin-regulated processes not associated with the inflammation process. Thus, use of high doses of most common NSAIDs can produce severe side effects, including life threatening ulcers, that limit their therapeutic potential. A popular current alternative to NSAIDs is the use of corticosteroids, which have even more drastic side effects, especially when long term therapy is involved.

Several families of pyrazole-containing compounds have been described as having anti-inflammatory activity. U.S. Patent No. 5,134,142 to Matsuo et al describes 1,5-diaryl-pyrazoles, and specifically 1-(4-fluorophenyl)-5-[(4-methylsulfonyl)phenyl]-3-trifluoromethyl-1H-pyrazole, as having anti-inflammatory activity.

U.S. Patent No. 3,984,431 to Gueremy et al describes derivatives of pyrazole-5-acetic acid as having anti-inflammatory action. Isofezolac (1,3,4-triphenyl-1H-pyrazole-5-acetic acid) is specifically described. 1,3,4-Triphenyl-5-(chloromethyl)-1H-pyrazole is described as an intermediate in the formation of the above mentioned derivatives. Isofezolac has been found to be as ulcerogenic as other common anti-inflammatory agents [J. Mizoule et al, Arch. int. Pharmacodyn., 238, 305 (1979)].

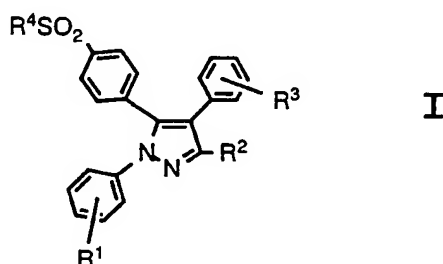
Little pharmaceutical activity has been described for 1,4,5-triphenyl-1H-pyrazolyl compounds. The rearrangement of epoxyketones has been observed to produce 1,4,5-triphenyl-1H-pyrazole [H. House et al, J. Amer. Chem. Soc., 79, 2490 (1957)]. Photochemical reactions of 4-(2-chlorophenyl)-1,5-diphenyl-1H-pyrazole and of 1,4,5-triphenyl-1H-pyrazole have been described [J. Grimshaw et al, J. Chem. Soc. Perkin. Trans. 1, 2096 (1977)]. The synthesis of a series of 1-aryl-4,5-diphenyl-1H-pyrazoles and a series of 1-aryl-3,4-diphenyl-1H-pyrazoles by reacting 2-phenylacrylophenone and arylhydrazines has been described [J. Wilshire, Aust. J. Chem., 27, 2041 (1974)]. Specifically 1-(4-methylphenyl)-4,5-diphenyl-1H-pyrazole is described. The rearrangement of epoxyphenylpropiophenone has been observed to produce 1-phenyl-4,5-substitutedphenyl-1H-pyrazoles, and specifically 1-phenyl-4,5-di(chlorophenyl)-1H-pyrazole [H. House et al, J. Amer. Chem. Soc., 83, 979 (1961)]. Triarylpyrazole compounds are prepared by reacting thioketoaldehydes and phenylhydrazines [M. Weissenfels et al, J. Prakt. Chem., 315, 873 (1973)] and specifically 4,5-bis(4-methoxyphenyl)-1-phenyl-1H-pyrazole. The reaction of phenylhydrazines with isoflavonoids to yield pyrazole compounds, such as 2-(1,4-diphenyl-1H-pyrazol-5-yl)-phenol has been described [V. Szabó et al, Acta Chim. Acad. Sci. Hung., 98, 457 (1979)].

The reaction of benzoin phenylhydrazone with aldehydes to produce 3-alkyl-1,4,5-triphenyl-1H-pyrazoles is described [H. Gnichtel et al, Liebigs Ann. Chem., 589 (1989)]. Specifically, 3-methyl-1,4,5-triphenyl-1H-pyrazole is described. The reaction of dinitrophenyl diketone derivatives with hydrazines has been studied, and 4-(2,4-dinitro)phenyl-1-(4-methylphenyl)-5-phenyl-3-methyl-1H-pyrazole has been described [I. Gambhir et al, J. Org. Chem., 27, 1899 (1962)].

1,4,5-Triphenyl-3-bromomethyl-1H-pyrazole is described as an intermediate in the synthesis of 1,4,5-triphenyl-1H-pyrazole-3-ethanoic acid, which is a potential anti-inflammatory agent [H. Biere, Arch. Pharm., 316, 608 (1983)].

DESCRIPTION OF THE INVENTION

A class of compounds useful in treating inflammation-related disorders is defined by Formula I:



wherein R^1 is one or more radicals
 10 independently selected from the group hydrido, halo, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, nitro, amino, N-monoalkylamino, N,N-dialkylamino, acylamino, acylaminoalkyl, haloalkyl, hydroxy and alkoxy; wherein R^2 is selected from hydrido, alkyl, cyano and haloalkyl;
 15 wherein R^3 is one or more radicals independently selected from the group hydrido, halo, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, nitro, amino, N-monoalkylamino, N,N-dialkylamino, acylamino, acylaminoalkyl, haloalkyl, hydroxy and alkoxy; and
 20 wherein R^4 is alkyl or amino; or a pharmaceutically-acceptable salt thereof.

Compounds of Formula I would be useful for the treatment of inflammation in a subject, and for treatment
 25 of other inflammation-associated disorders, such as an analgesic in the treatment of pain and headaches, or as an antipyretic for the treatment of fever. For example, compounds of Formula I would be useful to treat arthritis, including but not limited to rheumatoid
 30 arthritis, spondyloarthropathies, gouty arthritis, systemic lupus erythematosus, osteoarthritis and juvenile arthritis. Such compounds of Formula I would be useful in the treatment of asthma, bronchitis, menstrual cramps,

tendinitis, bursitis, and skin related conditions such as psoriasis, eczema, burns and dermatitis. Compounds of Formula I also would be useful to treat gastrointestinal conditions such as inflammatory bowel syndrome, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis. Compounds of Formula I would be useful in treating inflammation in such diseases as vascular diseases, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, myasthenia gravis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, hypersensitivity, conjunctivitis, gingivitis, swelling occurring after injury, myocardial ischemia, and the like. The compounds are useful as anti-inflammatory agents, such as for the treatment of arthritis, with the additional benefit of having significantly less harmful side effects.

A preferred class of compounds consists of those compounds of Formula I wherein R^1 is one or more radicals independently selected from the group hydrido, halo, lower alkyl, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, nitro, amino, N-monoalkylamino, N,N-dialkylamino, acylamino, acylaminoalkyl, lower haloalkyl, hydroxy and lower alkoxy; wherein R^2 is selected from hydrido, lower alkyl, cyano and lower haloalkyl; wherein R^3 is one or more radicals independently selected from the group hydrido, halo, lower alkyl, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, nitro, amino, N-monoalkylamino, N,N-dialkylamino, acylamino, acylaminoalkyl, lower haloalkyl, hydroxy and lower alkoxy; and wherein R^4 is lower alkyl or amino; or a pharmaceutically-acceptable salt thereof.

A class of compounds of particular interest consists of those compounds of Formula I wherein R^1 is one or more groups independently selected from hydrido, methyl, ethyl, methoxy, ethoxy, methylthio,

methysulfinyl, methysulfonyl, hydroxy, nitro, amino, N-methylamino, N,N-dimethylamino, acetamido, trifluoromethyl, bromo, iodo, fluoro and chloro; wherein R^2 is selected from hydrido, cyano, methyl, ethyl, propyl, trifluoromethyl, difluorochloromethyl, difluoromethyl, pentafluoroethyl and heptafluoropropyl; wherein R^3 is one or more groups independently selected from hydrido, methyl, ethyl, methoxy, ethoxy, methylthio, methysulfinyl, methysulfonyl, hydroxy, nitro, amino, N-methylamino, N,N-dimethylamino, acetamido, trifluoromethyl, bromo, iodo, fluoro and chloro; and wherein R^4 is methyl or amino; or a pharmaceutically-acceptable salt thereof.

15 A family of specific compounds of particular interest within Formula I consists of compounds and pharmaceutically-acceptable salts thereof as follows:

20 4-(4-fluorophenyl)-5-[4-(methysulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
4-(4-chlorophenyl)-5-[4-(methysulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
4-(4-bromophenyl)-5-[4-(methysulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
25 4-(4-iodophenyl)-5-[4-(methysulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
4-(2-fluorophenyl)-5-[4-(methysulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
4-(2-chlorophenyl)-5-[4-(methysulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
30 4-(2,4-difluorophenyl)-5-[4-(methysulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
4-(2,4-dichlorophenyl)-5-[4-(methysulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
35 5-[4-(methysulfonyl)phenyl]-1,4-diphenyl-3-(trifluoromethyl)-1H-pyrazole;
4-(4-methylphenyl)-5-[4-(methysulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;

- 4-(4-ethylphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 4-(4-tert-butylphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 5 4-(4-methylthiophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 4-(4-methylsulfinylphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 10 4,5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 4-(4-hydroxyphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 4-(4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 15 4-(4-nitrophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 4-(4-aminophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 20 4-(4-N-methylaminophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 4-(4-N,N-dimethylaminophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 25 4-(4-trifluoromethylphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 4-(4-acetamidophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 30 4-(4-[N-acetylamino]methylphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 35 1-(4-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;

- 1-(4-bromophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1-(4-iodophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 5 1-(4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1-(4-ethylphenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 10 1-(4-tert-butylphenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1-(4-methylthiophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1-(4-methylsulfinylphenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 15 1,5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1-(4-hydroxyphenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 20 1-(4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1-(4-nitrophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 25 1-(4-aminophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1-(4-N-methylaminophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1-(4-N,N-dimethylaminophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 30 1-(4-trifluoromethylphenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 35 1-(4-acetamidophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;

- 1-(4-[N-acetylamino]methylphenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-chlorodifluoromethyl-1H-pyrazole;
- 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-pentafluoroethyl-1H-pyrazole;
- 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-heptafluoropropyl-1H-pyrazole;
- 4-(4-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 4-(4-bromophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 4-(4-iodophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 4-(2-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 4-(2-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 4-(2,4-difluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 4-(2,4-dichlorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 5-[4-(methylsulfonyl)phenyl]-1,4-diphenyl-3-(difluoromethyl)-1H-pyrazole;
- 4-(4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 4-(4-ethylphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 4-(4-tert-butylphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 4-(4-methylthiophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 4-(4-methylsulfinylphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(difluoromethyl)-1H-pyrazole;

- 4,5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 4-(4-hydroxyphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 5 4-(4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 4-(4-nitrophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 10 4-(4-aminophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 4-(4-N-methylaminophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 4-(4-N,N-dimethylaminophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 15 4-(4-acetamidophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 4-(4-[N-acetylamino]methylphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 20 1-(4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 1-(4-ethylphenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 25 1-(4-tert-butylphenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 1-(4-methylthiophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 30 1-(4-methylsulfinylphenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 1,5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 35 1-(4-hydroxyphenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 1-(4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(difluoromethyl)-1H-pyrazole;

- 1-(4-nitrophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 1-(4-aminophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 5 1-(4-N-methylaminophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 1-(4-N,N-dimethylaminophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 10 1-(4-acetamidophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 1-(4-[N-acetylamino]methylphenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 15 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-1H-pyrazole;
- 4-(4-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-1H-pyrazole;
- 20 4-(4-bromophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-1H-pyrazole;
- 1,4-bis(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;
- 1,4-bis(4-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;
- 25 1,4-bis(4-bromophenyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;
- 1,4-bis(4-iodophenyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;
- 30 1,4-bis(2-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;
- 1,4-bis(2-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;
- 1,4-bis(2,4-difluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;
- 35 1,4-bis(2,4-dichlorophenyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;

- 5-[4-(methanesulfonyl)phenyl]-1,4-diphenyl-3-(trifluoromethyl)-1H-pyrazole;
1,4-bis(4-methylphenyl)-5-[4-(methanesulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;
5 1,4-bis(4-ethylphenyl)-5-[4-(methanesulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;
1,4-bis(4-tert-butylphenyl)-5-[4-(methanesulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;
1,4-bis(4-methylthiophenyl)-5-[4-(methanesulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;
10 1,4-bis(4-methanesulfinylphenyl)-5-[4-(methanesulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;
1,4,5-tris[4-(methanesulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;
15 1,4-bis(4-hydroxyphenyl)-5-[4-(methanesulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;
1,4-bis(4-methoxyphenyl)-5-[4-(methanesulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;
1,4-bis(4-nitrophenyl)-5-[4-(methanesulfonyl)phenyl]-
20 3-(trifluoromethyl)-1H-pyrazole;
1,4-bis(4-aminophenyl)-5-[4-(methanesulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;
1,4-bis(4-N-methylaminophenyl)-5-[4-(methanesulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;
25 1,4-bis(4-N,N-dimethylaminophenyl)-5-[4-(methanesulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;
1,4-bis(4-trifluoromethylphenyl)-5-[4-(methanesulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;
1,4-bis(4-acetamidophenyl)-5-[4-(methanesulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;
30 1,4-bis(4-[N-acetylamino]methylphenyl)-5-[4-(methanesulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;
1,4-bis(4-fluorophenyl)-5-[4-(methanesulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;
35 1,4-bis(4-fluorophenyl)-5-[4-(methanesulfonyl)phenyl]-3-chlorodifluoromethyl-1H-pyrazole;

- 1,4-bis(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3-pentafluoroethyl-1H-pyrazole;
1,4-bis(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3-heptafluoropropyl-1H-pyrazole;
5 1,4-bis(4-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;
1,4-bis(4-bromophenyl)-5-[4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;
10 1,4-bis(4-iodophenyl)-5-[4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;
1,4-bis(2-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;
1,4-bis(2-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;
15 4-(2,4-difluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(difluoromethyl)-1H-pyrazole;
4-(2,4-dichlorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(difluoromethyl)-1H-pyrazole;
5-[4-(methylsulfonyl)phenyl]-1,4-diphenyl-3-(difluoromethyl)-1H-pyrazole;
20 1,4-bis(4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;
1,4-bis(4-ethylphenyl)-5-[4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;
25 1,4-bis(4-tert-butylphenyl)-5-[4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;
1,4-bis(4-methylthiophenyl)-5-[4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;
1,4-bis(4-methylsulfinylphenyl)-5-[4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;
30 1,4,5-tris[4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;
1,4-bis(4-hydroxyphenyl)-5-[4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;
35 1,4-bis(4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;
1,4-bis(4-nitrophenyl)-5-[4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;

- 1,4-bis(4-aminophenyl)-5-[4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;
- 1,4-bis(4-N-methylaminophenyl)-5-[4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;
- 5 1,4-bis(4-N,N-dimethylaminophenyl)-5-[4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;
- 1,4-bis(4-difluoromethylphenyl)-5-[4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;
- 1,4-bis(4-acetamidophenyl)-5-[4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;
- 10 1,4-bis(4-[N-acetylamino]methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazole;
- 1,4-bis(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1H-pyrazole;
- 15 1,4-bis(4-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-1H-pyrazole;
- 1,4-bis(4-bromophenyl)-5-[4-(methylsulfonyl)phenyl]-1H-pyrazole;
- 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(methyl)-1H-pyrazole;
- 20 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(ethyl)-1H-pyrazole;
- 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(propyl)-1H-pyrazole;
- 25 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(cyano)-1H-pyrazole;
- 4-[4-(4-fluorophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 30 4-[4-(4-chlorophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-bromophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-iodophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 35 4-[4-(2-fluorophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

- 4-[4-(2-chlorophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(2,4-difluorophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 5 4-[4-(2,4-dichlorophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1,4-diphenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-methylphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 10 4-[4-(4-ethylphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-tert-butylphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 15 4-[4-(4-methylthiophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-methylsulfinylphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4,1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 20 4-[4-(4-hydroxyphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-methoxyphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 25 4-[4-(4-nitrophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-aminophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-N-methylaminophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 30 4-[4-(4-N,N-dimethylaminophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-trifluoromethylphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 35 4-[4-(4-acetamidophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-[N-acetylamino]methylphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

- 4-[1-(4-fluorophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1-(4-chlorophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 5 4-[1-(4-bromophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1-(4-iodophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1-(4-methylphenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 10 4-[1-(4-ethylphenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1-(4-tert-butylphenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 15 4-[1-(4-methylthiophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1-(4-methylsulfinylphenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1,4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 20 4-[1-(4-hydroxyphenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1-(4-methoxyphenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 25 4-[1-(4-nitrophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1-(4-aminophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1-(4-N-methylaminophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 30 4-[1-(4-N,N-dimethylaminophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1-(4-trifluoromethylphenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 35 4-[1-(4-acetamidophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1-(4-[N-acetylamino]methylphenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

- 4-[4-(4-fluorophenyl)-1-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-fluorophenyl)-1-phenyl-3-chlorodifluoromethyl-1H-pyrazol-5-yl]benzenesulfonamide;
- 5 4-[4-(4-fluorophenyl)-1-phenyl-3-pentafluoroethyl-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-fluorophenyl)-1-phenyl-3-heptafluoropropyl-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-chlorophenyl)-1-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 10 4-[4-(4-bromophenyl)-1-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-iodophenyl)-1-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 15 4-[4-(2-fluorophenyl)-1-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(2-chlorophenyl)-1-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(2,4-difluorophenyl)-1-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 20 4-[4-(2,4-dichlorophenyl)-1-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1,4-diphenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 25 4-[4-(4-methylphenyl)-1-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-ethylphenyl)-1-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-tert-butylphenyl)-1-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 30 4-[4-(4-methylthiophenyl)-1-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-methylsulfinylphenyl)-1-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 35 4-[4,1-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-hydroxyphenyl)-1-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

- 4-[4-(4-methoxyphenyl)-1-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-nitrophenyl)-1-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 5 4-[4-(4-aminophenyl)-1-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-N-methylaminophenyl)-1-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-N,N-dimethylaminophenyl)-1-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 10 (difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-acetamidophenyl)-1-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-[N-acetylamino]methylphenyl)-1-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 15 4-[1-(4-methylphenyl)-4-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1-(4-ethylphenyl)-4-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1-(4-tert-butylphenyl)-4-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 20 (difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1-(4-methylthiophenyl)-4-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1-(4-methylsulfinylphenyl)-4-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 25 4-[1,4-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1-(4-hydroxyphenyl)-4-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1-(4-methoxyphenyl)-4-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 30 1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1-(4-nitrophenyl)-4-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1-(4-aminophenyl)-4-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 35 4-[1-(4-N-methylaminophenyl)-4-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1-(4-N,N-dimethylaminophenyl)-4-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

- 4-[1-(4-acetamidophenyl)-4-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[1-(4-[N-acetylamino]methylphenyl)-4-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
5 4-[4-(4-fluorophenyl)-1-phenyl-1H-pyrazol-5-yl]benzenesulfonamide;
4-[4-(4-chlorophenyl)-1-phenyl-1H-pyrazol-5-yl]benzenesulfonamide;
4-[4-(4-bromophenyl)-1-phenyl-1H-pyrazol-5-yl]benzenesulfonamide;
10 4-[1,4-bis(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[1,4-bis(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
15 4-[1,4-bis(4-bromophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[1,4-bis(4-iodophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[1,4-bis(2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
20 4-[1,4-bis(2-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[1,4-bis(2,4-difluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
25 4-[1,4-bis(2,4-dichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[1,4-diphenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[1,4-bis(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
30 4-[1,4-bis(4-ethylphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[1,4-bis(4-tert-butylphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
35 4-[1,4-bis(4-methylthiophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[1,4-bis(4-methylsulfinylphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

- 4-[1,4,5-tris[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1,4-bis(4-hydroxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 5 4-[1,4-bis(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1,4-bis(4-nitrophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 10 4-[1,4-bis(4-aminophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1,4-bis(4-N-methylaminophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1,4-bis(4-N,N-dimethylaminophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 15 4-[1,4-bis(4-trifluoromethylphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1,4-bis(4-acetamidophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1,4-bis(4-[N-acetylamino]methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 20 4-[1,4-bis(4-fluorophenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1,4-bis(4-fluorophenyl)-3-chlorodifluoromethyl-1H-pyrazol-5-yl]benzenesulfonamide;
- 25 4-[1,4-bis(4-fluorophenyl)-3-pentafluoroethyl-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1,4-bis(4-fluorophenyl)-3-heptafluoropropyl-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1,4-bis(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 30 4-[1,4-bis(4-bromophenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1,4-bis(4-iodophenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 35 4-[1,4-bis(2-fluorophenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1,4-bis(2-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

- 4-[4-(2,4-difluorophenyl)-1-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(2,4-dichlorophenyl)-1-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 5 4-[1,4-diphenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1,4-bis(4-methylphenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1,4-bis(4-ethylphenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 10 4-[1,4-bis(4-tert-butylphenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1,4-bis(4-methylthiophenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 15 4-[1,4-bis(4-methylsulfinylphenyl)-5-[4-(methylsulfonyl)phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1,4,5-tris[4-(methylsulfonyl)phenyl]-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 20 4-[1,4-bis(4-hydroxyphenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1,4-bis(4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1,4-bis(4-nitrophenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 25 4-[1,4-bis(4-aminophenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1,4-bis(4-N-methylaminophenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 30 4-[1,4-bis(4-N,N-dimethylaminophenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1,4-bis(4-difluoromethylphenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1,4-bis(4-acetamidophenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 35 4-[1,4-bis(4-[N-acetylamino]methylphenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

4-[1,4-bis(4-fluorophenyl)-1H-pyrazol-5-yl]benzenesulfonamide;

4-[1,4-bis(4-chlorophenyl)-1H-pyrazol-5-yl]benzenesulfonamide;

5 4-[1,4-bis(4-bromophenyl)-1H-pyrazol-5-yl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-1-phenyl-3-(methyl)-1H-pyrazol-5-yl]benzenesulfonamide;

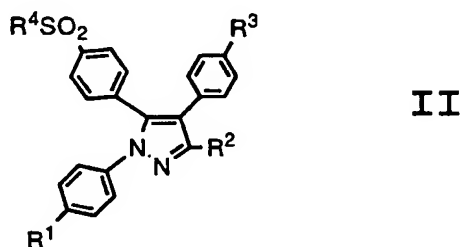
10 4-[4-(4-fluorophenyl)-1-phenyl-3-(ethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-1-phenyl-3-(propyl)-1H-pyrazol-5-yl]benzenesulfonamide; and

4-[4-(4-fluorophenyl)-1-phenyl-3-(cyano)-1H-pyrazol-5-yl]benzenesulfonamide.

15

Within Formula I there is a subclass of compounds of high interest represented by Formula II:



20

wherein R¹ is selected from the group hydrido, halo, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, nitro, amino, N-monoalkylamino, N,N-dialkylamino, acylamino, acylaminoalkyl, haloalkyl, hydroxy and alkoxy; wherein R²
 25 is selected from hydrido, alkyl, cyano and haloalkyl; wherein R³ is selected from the group hydrido, halo, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, nitro, amino, N-monoalkylamino, N,N-dialkylamino, acylamino, acylaminoalkyl, haloalkyl, hydroxy and alkoxy; and
 30 wherein R⁴ is alkyl or amino; or a pharmaceutically-acceptable salt thereof.

A preferred class of compounds consists of those compounds of Formula II wherein R^1 is selected from the group hydrido, halo, lower alkyl, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, nitro, amino, N-monoalkylamino, N,N-dialkylamino, acylamino, acylaminoalkyl, lower haloalkyl, hydroxy and lower alkoxy; wherein R^2 is selected from hydrido, lower alkyl, cyano and lower haloalkyl; wherein R^3 is selected from the group hydrido, halo, lower alkyl, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, nitro, amino, N-monoalkylamino, N,N-dialkylamino, acylamino, acylaminoalkyl, lower haloalkyl, hydroxy and lower alkoxy; and wherein R^4 is lower alkyl or amino; or a pharmaceutically-acceptable salt thereof.

A class of compounds of particular interest consists of those compounds of Formula II wherein R^1 is selected from hydrido, methyl, ethyl, methoxy, ethoxy, methylthio, methylsulfinyl, methylsulfonyl, hydroxy, nitro, amino, N-methylamino, N,N-dimethylamino, acetamido, trifluoromethyl, bromo, iodo, fluoro and chloro; wherein R^2 is selected from hydrido, cyano, methyl, ethyl, propyl, trifluoromethyl, difluorochloromethyl, difluoromethyl, pentafluoroethyl and heptafluoropropyl; wherein R^3 is selected from hydrido, methyl, ethyl, methoxy, ethoxy, methylthio, methylsulfinyl, methylsulfonyl, hydroxy, nitro, amino, N-methylamino, N,N-dimethylamino, acetamido, trifluoromethyl, bromo, iodo, fluoro and chloro; and wherein R^4 is methyl or amino; or a pharmaceutically-acceptable salt thereof.

A family of specific compounds of particular interest within Formula II consists of compounds and pharmaceutically-acceptable salts thereof as follows:

4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;

- 4-(4-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 4-(4-bromophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 5 4-(4-iodophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 5-[4-(methylsulfonyl)phenyl]-1,4-diphenyl-3-(trifluoromethyl)-1H-pyrazole;
- 4-(4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 10 4-(4-methylthiophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 4-(4-methylsulfinylphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 15 4-(4-hydroxyphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 4-(4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 20 4-(4-nitrophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 4-(4-aminophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 4-(4-N-methylaminophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 25 4-(4-N,N-dimethylaminophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 4-(4-trifluoromethylphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 30 4-(4-acetamidophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 35 4-(4-[N-acetylamino]methylphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;

- 1-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1-(4-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 5 1-(4-bromophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1-(4-iodophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1-(4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 10 1-(4-methylthiophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1-(4-hydroxyphenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 15 1-(4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1-(4-nitrophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 20 1-(4-aminophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1-(4-N-methylaminophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 25 1-(4-N,N-dimethylaminophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1-(4-trifluoromethylphenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 30 1-(4-acetamidophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-1H-pyrazole;
- 35 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(methyl)-1H-pyrazole;

- 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(cyano)-1H-pyrazole;
1,4-bis(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;
5 5-[4-(methylsulfonyl)phenyl]-1,4-diphenyl-3-(difluoromethyl)-1H-pyrazole;
- 4-[4-(4-fluorophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
10 4-[4-(4-chlorophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[4-(4-bromophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[4-(4-iodophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
15 4-[1,4-diphenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[4-(4-methylphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
20 4-[4-(4-methylthiophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[4-(4-methylsulfinylphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[4-(4-hydroxyphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
25 4-[4-(4-methoxyphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[4-(4-nitrophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
30 4-[4-(4-aminophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[4-(4-N-methylaminophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[4-(4-N,N-dimethylaminophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
35 4-[4-(4-trifluoromethylphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

- 4-[4-(4-acetamidophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[4-(4-[N-acetylamino]methylphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
5 4-[1-(4-fluorophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[1-(4-chlorophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[1-(4-bromophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
10 4-[1-(4-iodophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[1-(4-methylphenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
15 4-[1-(4-methylthiophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[1-(4-hydroxyphenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[1-(4-methoxyphenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
20 4-[1-(4-nitrophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[1-(4-aminophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
25 4-[1-(4-N-methylaminophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[1-(4-N,N-dimethylaminophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[1-(4-trifluoromethylphenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
30 4-[1-(4-acetamidophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[4-(4-fluorophenyl)-1-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
35 4-[4-(4-fluorophenyl)-1-phenyl-1H-pyrazol-5-yl]benzenesulfonamide;
4-[4-(4-fluorophenyl)-1-phenyl-3-(methyl)-1H-pyrazol-5-yl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-1-phenyl-3-(cyano)-1H-pyrazol-5-yl]benzenesulfonamide;

4-[1,4-bis(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide; and

5 4-[1,4-diphenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide.

Where the term "alkyl" is used, either alone or within other terms such as "haloalkyl", "alkoxyalkyl" and
10 "hydroxyalkyl", embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl
15 radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, and the like. The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical
20 may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene (-CH₂-) radical. The term "halo" means halogens such as fluorine, chlorine, bromine or iodine atoms. The term "haloalkyl" embraces
25 radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for example, may have either a bromo, chloro or a fluoro atom
30 within the radical. Dihalo radicals have two halo radicals or a combination of different halo radicals and polyhaloalkyl radicals have more than two of the same halo atoms or a combination of different halo radicals. Most preferred are lower haloalkyl radicals having one to
35 about six carbon atoms. The term "alkoxy" embraces linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. Most preferred are lower alkoxy radicals having one to about six carbon

atoms. The "alkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkoxy or haloalkoxyalkyl radicals. The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to about ten carbon atoms attached to a divalent sulfur atom, such as a methythio radical. Most preferred are lower alkylthio radicals having one to about six carbon atoms. The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals $-SO_2-$. "Alkylsulfonyl" embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. Most preferred are lower alkylsulfonyl radicals having one to about six carbon atoms. The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent $-S(=O)-$ atom. Most preferred are lower alkylsulfinyl radicals having one to about six carbon atoms. The terms "aminosulfonyl", "sulfamyl" and "sulfonamidyl" denote a sulfonyl radical substituted with an amine radical, forming a sulfonamide ($-SO_2NH_2$). The terms "N-alkylamino" and "N,N-dialkylamino" denote amino groups which have been substituted with one alkyl radical and with two alkyl radicals, respectively. Most preferred are lower alkylamino and dialkylamino radicals having alkyl radicals of one to about six carbon atoms. The term "acyl", whether used alone, or within a term such as "acylamino", denotes a radical provided by the residue after removal of hydroxyl from an organic acid. The term "acylamino" embraces an amino radical substituted with an acyl group. An examples of an "acylamino" radical is acetyl amino ($CH_3C(=O)-NH-$). The term "acylaminoalkyl" embraces an alkyl radical substituted with an acylamino group, as defined above. An example of an "acylaminoalkyl" radical is (acetyl amino)methyl ($CH_3C(=O)NHCH_2-$).

The present invention comprises a pharmaceutical composition for the treatment of inflammation and inflammation-associated disorders, such as arthritis, comprising a therapeutically-effective amount of a compound of Formula I and II in association with at least one pharmaceutically-acceptable carrier, adjuvant or diluent.

The present invention also comprises a therapeutic method of treating inflammation or inflammation-associated disorders in a subject, the method comprising administering to a subject having such inflammation or disorder a therapeutically-effective amount of a compound of Formula I and II.

Also included in the family of compounds of Formula I are the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formula I may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, 2-hydroxyethanesulfonic, toluenesulfonic, sulfanilic, cyclohexylaminosulfonic,

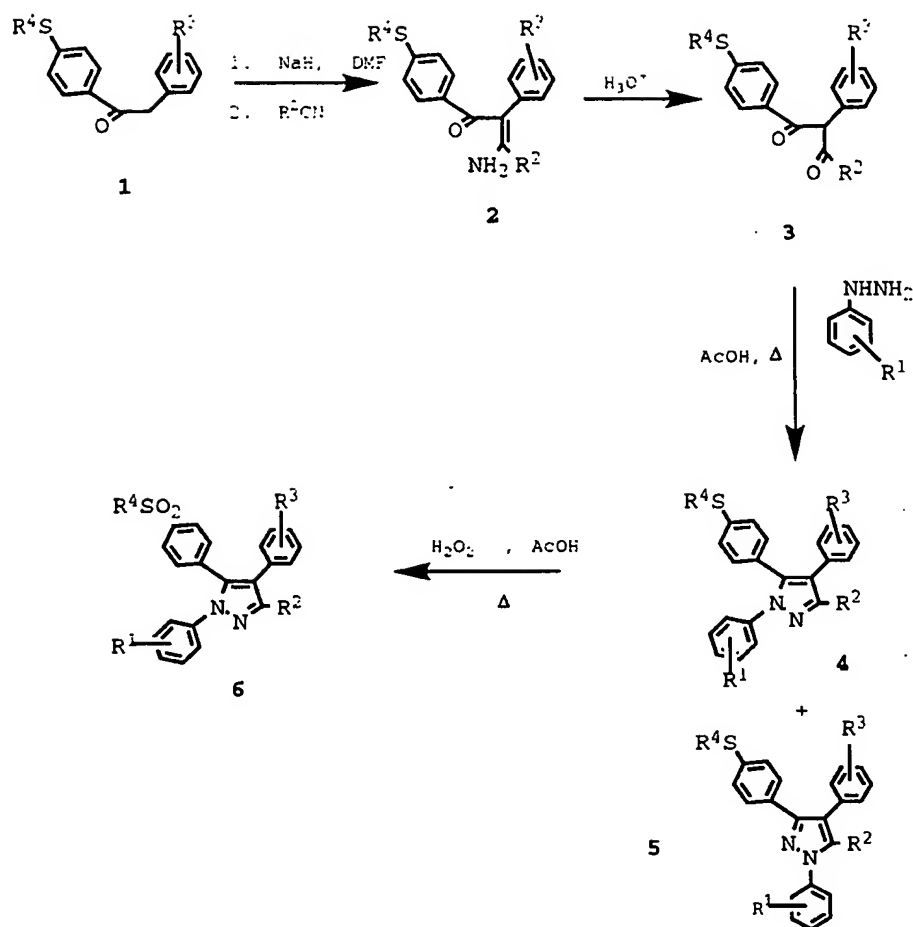
stearic, algenic, β -hydroxybutyric, salicyclic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formula I include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound of Formula I by reacting, for example, the appropriate acid or base with the compound of Formula I.

GENERAL SYNTHETIC PROCEDURES

The compounds of the invention can be synthesized according to the following procedures of Schemes I-III, wherein the R¹-R⁴ substituents are as defined for Formula I, above, except where further noted.

32

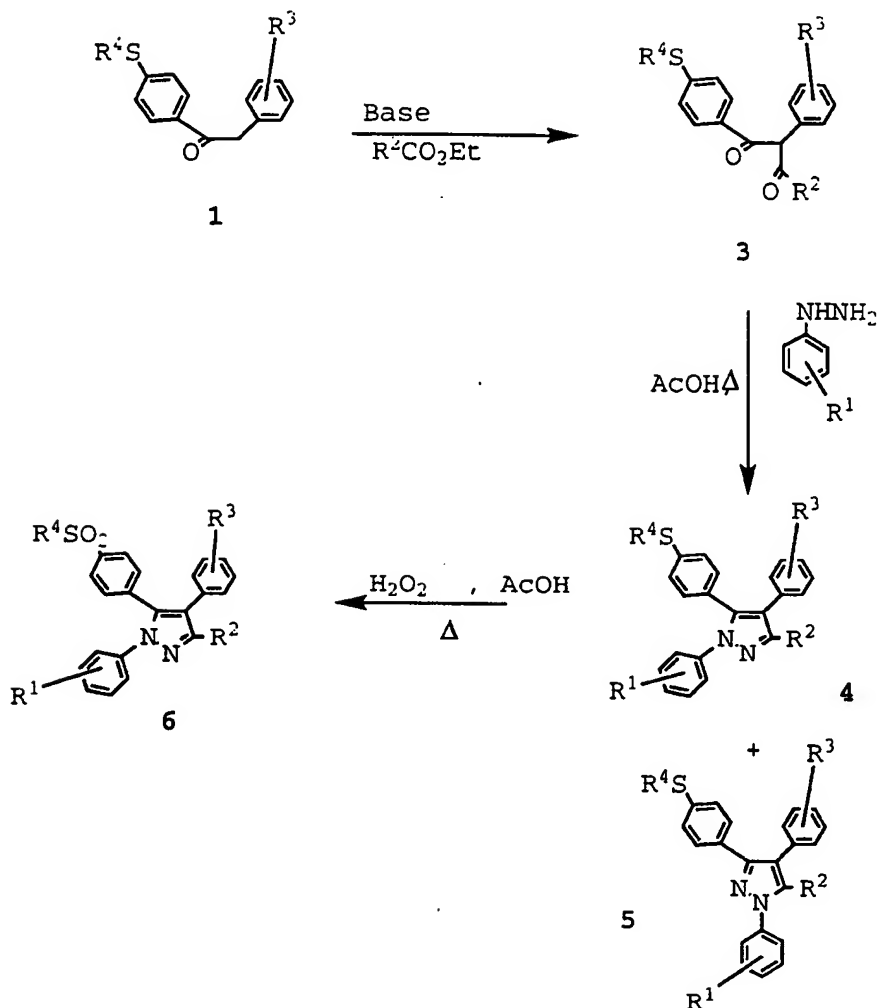
Scheme I



In step 1 of synthetic Scheme I, 1-[(4-alkylthio)phenyl]-2-[R³-phenyl]ethanone 1 is reacted with sodium hydride in an anhydrous aprotic solvent, such as dimethylformamide or tetrahydrofuran to form the sodium enolate. Reaction of the enolate with gaseous haloalkylnitrile yields the enamine 2. In step 2, the enamine 2 is hydrolyzed with 6N hydrochloric acid to give the 1,3-diketone 3. In step 3, reaction of the diketone 3 with a substituted or unsubstituted phenylhydrazine gives the 5-[4-(alkylthio)phenylpyrazole] 4 and its position isomer 5. Separation of the desired product from its isomer can be achieved by high performance liquid chromatography (HPLC). In step 4, oxidation of pyrazole 4 with hydrogen

peroxide yields 5-[4-(alkylsulfonyl)phenyl]-1*H*-pyrazole compounds 6 embraced by Formula I.

Scheme II

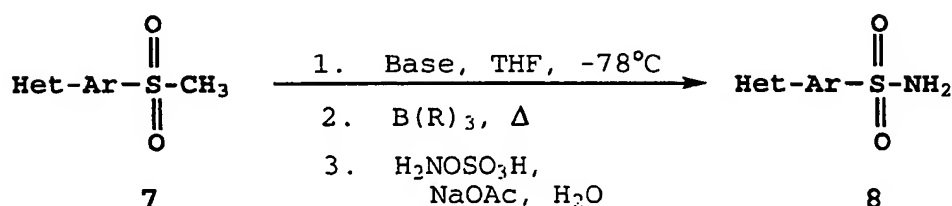


Alternatively, the compounds embraced by Formula I may be prepared, as shown in Scheme II. In step 1, 1-[(4-alkylthio)phenyl]-2-[R³-phenyl]ethanone 1 is reacted with strong base, such as sodium methoxide, lithium diisopropylamide (LDA), lithium 2,2,6,6-tetramethylpiperidide or sodium bis(trimethylsilyl)amide, and an ester or ester equivalent, such as an acyl imidazole, under Claisen condensation conditions, to give the 1,3-diketone 3. In step 2, reaction of the diketone 3 with a substituted or

unsubstituted phenylhydrazine gives the (5-[4-alkylthio)phenyl]-1H-pyrazole 4 and its position isomer 5. Separation of the desired product from its isomer can be achieved by high performance liquid chromatography (HPLC). In step 4, oxidation of pyrazole 4 with hydrogen peroxide yields 5-[4-(alkylsulfonyl)phenyl]-1-H-pyrazole compounds 6 embraced by Formula I.

Scheme III

10



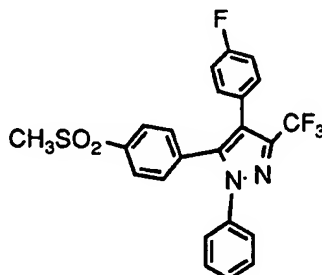
Synthetic Scheme III shows the three step procedure used to prepare sulfonamide antiinflammatory agents 8 from their corresponding methyl sulfones 7. In step one, THF solutions of the methyl sulfones 7 at -78°C are treated with an alkylolithium reagent, e.g., methyllithium, n-butyllithium, etc. In step two, the anions generated in step one are treated with an organoborane, e.g., triethylborane, tributylborane, etc., at -78°C then allowed to warm to ambient temperature prior to stirring at reflux. In step three, an aqueous solution of sodium acetate and hydroxylamine-O-sulfonic acid is added to provide the corresponding sulfonamide antiinflammatory agents 8 of this invention.

The following examples contain detailed descriptions of the methods of preparation of compounds of Formula I. These detailed descriptions fall within the scope, and serve to exemplify, the above described General Synthetic Procedures which form part of the invention. These detailed descriptions are presented for

illustrative purposes only and are not intended as a restriction on the scope of the invention. All parts are by weight and temperatures are in Degrees centigrade unless otherwise indicated.

5

EXAMPLE 1



10

4-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)pyrazole.

15 Step 1: Preparation of 3-amino-4,4,4-trifluoro-2-(4-fluorophenyl)-1-[4-(methylthio)phenyl]-2-buten-1-one

To a mixture of 2.6 g (0.087 mol) of 80% sodium hydride oil dispersion and 10 mL of dimethylformamide (DMF) was added, under nitrogen, a solution of 21.4 g (0.082 mol) of 2-(4-fluorophenyl)-1-[4-(methylthio)phenyl]ethanone in 150 ml of DMF for 30 minutes. The resulting mixture was stirred at room temperature for 1 hour. To the above mixture was passed 10 g (0.11 mol) of gaseous trifluoroacetonitrile for 40 minutes. The reaction mixture was analyzed by TLC. The reaction mixture was poured into 400 mL of water and the solid precipitate was filtered and air dried. The solid precipitate was stirred with 300 mL of ether. The insoluble material was filtered to give 6.0 g (28%) of unreacted 2-(4-fluorophenyl)-1-[4-(methylthio)phenyl]ethanone. The ether filtrate was dried over MgSO_4 and concentrated in vacuo. The ether filtrate was recrystallized from 5% ethyl acetate-hexane

to give 12.3 g of a mixture (6:1) of 3-amino-4,4,4-trifluoro-2-(4-fluorophenyl)-1-[4-(methylthio)phenyl]-2-buten-1-one and 2-(4-fluorophenyl)-1-[4-(methylthio)phenyl]ethanone. This solid was heated with 100 mL of ether and cooled. The insoluble solid of 2-(4-fluorophenyl)-1-[4-(methylthio)phenyl]ethanone (0.5 g) was filtered. The ether filtrate was concentrated and the residue was recrystallized from 10% ethyl acetate-hexane to give 10.5 g (36%) of 3-amino-4,4,4-trifluoro-2-(4-fluorophenyl)-1-[4-(methylthio)phenyl]-2-buten-1-one, mp 122.5-124.5 °C. The combined ethyl acetate-hexane mother liquor was concentrated and the residue was purified by HPLC (10% ethyl acetate-hexane). The second fraction gave an additional 2.6 g (9%) of 3-amino-4,4,4-trifluoro-2-(4-fluorophenyl)-1-[4-(methylthio)phenyl]-2-buten-1-one after recrystallization from 5% ethyl acetate-hexane.

Step 2: Preparation of 4-(4-fluorophenyl)-3-[4-(methylthio)phenyl]-1-phenyl-5-(trifluoromethyl)pyrazole and 4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-1-phenyl-3-(trifluoromethyl)pyrazole.

A mixture of 4.0 g of product of step 1, 40 mL of ether, and 40 mL of 6 N hydrochloric acid was stirred at room temperature for 4 days. The ether layer was dried over magnesium sulfate and concentrated in vacuo to give 4.0 g of crude 2-(4-fluorophenyl)-1-[4-(methylthio)phenyl]-4,4,4-trifluoro-1,3-butandione. A mixture of 0.22 g (0.59 mmol) of this product, 0.09 g of phenylhydrazine, and 10 mL of glacial acetic acid was heated at 80 °C for 18 hours and poured into water. The insoluble solid was purified by HPLC (10% ethyl acetate-hexane) to give 8 mg of 4-(4-fluorophenyl)-3-[4-(methylthio)phenyl]-1-phenyl-5-(trifluoromethyl)pyrazole and 140 mg of 4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-1-phenyl-3-(trifluoromethyl)pyrazole.

Step 3: Preparation of 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)pyrazole.

5

To a mixture of 140 mg of 4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-1-phenyl-3-(trifluoromethyl)pyrazole and 30 mL of glacial acetic acid was added 4.1 g of 30% hydrogen peroxide. The reaction mixture was stirred at room temperature for 18 hours, heated at 80 °C for 8 hours, and poured into water. The insoluble solid was filtered and air dried to give 150 mg of solid, mp 201.5-203 °C.

15

BIOLOGICAL EVALUATION

Rat Carrageenan Foot Pad Edema Test

The carrageenan foot edema test was performed with materials, reagents and procedures essentially as described by Winter, et al., (Proc. Soc. Exp. Biol. Med., 111, 544 (1962)). Male Sprague-Dawley rats were selected in each group so that the average body weight was as close as possible. Rats were fasted with free access to water for over sixteen hours prior to the test. The rats were dosed orally (1 mL) with compounds suspended in vehicle containing 0.5% methylcellulose and .025% surfactant, or with vehicle alone. One hour later a subplantar injection of 0.1 mL of 1% solution of carrageenan/sterile 0.9% saline was administered and the volume of the injected foot was measured with a displacement plethysmometer connected to a pressure transducer with a digital indicator. Three hours after the injection of the carrageenan, the volume of the foot was again measured. The average foot swelling in a group of drug-treated animals was compared with that of a group of placebo-treated animals and the percentage inhibition of edema was determined (Otterness and Bliven, Laboratory

Models for Testing NSAIDs. in Non-steroidal Anti-Inflammatory Drugs, (J. Lombardino, ed. 1985)). Results are shown in Table I.

5

TABLE I.

	RAT PAW EDEMA
	% Inhibition
	@ 10mg/kg body weight
10	
Example 1	20

Also embraced within this invention is a class
15 of pharmaceutical compositions comprising one or more
compounds of Formula I in association with one or more
non-toxic, pharmaceutically acceptable carriers and/or
diluent and/or adjuvants (collectively referred to
herein as "carrier" materials) and, if desired, other
20 active ingredients. The compounds of the present
invention may be administered by any suitable route,
preferably in the form of a pharmaceutical composition
adapted to such a route, and in a dose effective for the
treatment intended. The compounds and composition may,
25 for example, be administered intravascularly,
intraperitoneally, subcutaneously, intramuscularly or
topically.

For oral administration, the pharmaceutical
30 composition may be in the form of, for example, a tablet,
capsule, suspension or liquid. The pharmaceutical
composition is preferably made in the form of a dosage
unit containing a particular amount of the active
ingredient. Examples of such dosage units are tablets or
35 capsules. The active ingredient may also be administered
by injection as a composition wherein, for example,
saline, dextrose or water may be used as a suitable
carrier.

The amount of therapeutically active compound that is administered and the dosage regimen for treating a disease condition with the compounds and/or

5 compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the disease, the route and frequency of administration, and the particular compound employed, and thus may vary widely.

10 The pharmaceutical compositions may contain active ingredient in the range of about 0.1 to 2000 mg, preferably in the range of about 0.5 to 500 mg and most preferably between about 1 and 100 mg. A daily dose of about 0.01 to 100 mg/kg body weight, preferably between

15 about 0.1 and about 50 mg/kg body weight and most preferably from about 1 to 20 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day.

20 For therapeutic purposes, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the compounds may be admixed with lactose, sucrose, starch powder,

25 cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then

30 tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of

35 aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use

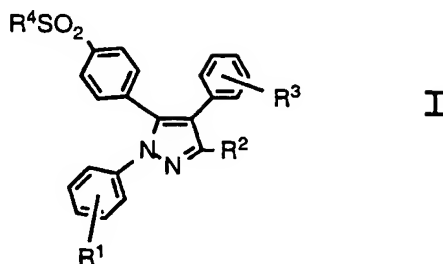
in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations.

What is claimed is:

1. A compound of Formula I

5



wherein R^1 is one or more radicals
independently selected from the group hydrido, halo,
10 alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, nitro,
amino, N-monoalkylamino, N,N-dialkylamino, acylamino,
acylaminoalkyl, haloalkyl, hydroxy and alkoxy;

wherein R^2 is selected from hydrido, alkyl,
cyano and haloalkyl;

15 wherein R^3 is one or more radicals
independently selected from the group hydrido, halo,
alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, nitro,
amino, N-monoalkylamino, N,N-dialkylamino, acylamino,
acylaminoalkyl, haloalkyl, hydroxy and alkoxy; and

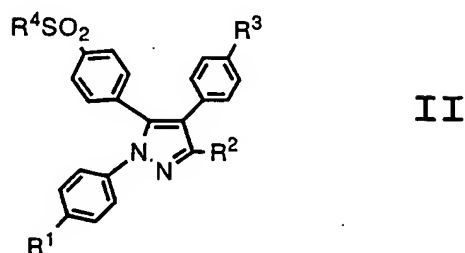
20 wherein R^4 is alkyl or amino; or a
pharmaceutically-acceptable salt thereof.

2. Compound of Claim 1 wherein R^1 is one or
more radicals independently selected from the group
25 hydrido, halo, lower alkyl, lower alkylthio, lower
alkylsulfinyl, lower alkylsulfonyl, nitro, amino, N-
monoalkylamino, N,N-dialkylamino, acylamino,
acylaminoalkyl, lower haloalkyl, hydroxy and lower
alkoxy; wherein R^2 is selected from hydrido, lower alkyl,
30 cyano and lower haloalkyl; wherein R^3 is one or more
radicals independently selected from the group hydrido,
halo, lower alkyl, lower alkylthio, lower alkylsulfinyl,
lower alkylsulfonyl, nitro, amino, N-monoalkylamino, N,N-

dialkylamino, acylamino, acylaminoalkyl, lower haloalkyl, hydroxy and lower alkoxy; and wherein R⁴ is lower alkyl or amino; or a pharmaceutically-acceptable salt thereof.

- 5 3. Compound of Claim 2 or a pharmaceutically-
acceptable salt thereof, wherein R¹ is one or more groups
independently selected from hydrido, methyl, ethyl,
methoxy, ethoxy, methylthio, methylsulfinyl,
methylsulfonyl, hydroxy, nitro, amino, N-methylamino,
10 acetamido, trifluoromethyl, fluoro, bromo, iodo and
chloro; wherein R² is selected from hydrido, cyano,
methyl, ethyl, propyl, isopropyl, butyl, trifluoromethyl,
difluorochloromethyl, difluoromethyl, pentafluoroethyl
and heptafluoropropyl; wherein R³ is one or more groups
15 independently selected from hydrido, methyl, ethyl,
methoxy, ethoxy, methylthio, methylsulfinyl,
methylsulfonyl, hydroxy, nitro, amino, N-methylamino,
acetamido, trifluoromethyl, fluoro, bromo, iodo and
chloro; and wherein R⁴ is methyl or amino.

4. A compound of Formula II



- 5 wherein R^1 is selected from the group hydrido, halo, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, nitro, amino, N-monoalkylamino, N,N-dialkylamino, acylamino, acylaminoalkyl, haloalkyl, hydroxy and alkoxy; wherein R^2 is selected from hydrido, alkyl,
- 10 cyano and haloalkyl; wherein R^3 is selected from the group hydrido, halo, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, nitro, amino, N-monoalkylamino, N,N-dialkylamino, acylamino, acylaminoalkyl, haloalkyl, hydroxy and alkoxy;
- 15 and wherein R^4 is alkyl or amino; or a pharmaceutically-acceptable salt thereof.

5. Compound of Claim 4 wherein R^1 is selected
- 20 from the group hydrido, halo, lower alkyl, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, nitro, amino, N-monoalkylamino, N,N-dialkylamino, acylamino, acylaminoalkyl, lower haloalkyl, hydroxy and lower alkoxy; wherein R^2 is selected from hydrido, cyano,
- 25 lower alkyl and lower haloalkyl; wherein R^3 is selected from the group hydrido, halo, lower alkyl, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, nitro, amino, N-monoalkylamino, N,N-dialkylamino, acylamino, acylaminoalkyl, lower haloalkyl, hydroxy and
- 30 lower alkoxy; and wherein R^4 is lower alkyl or amino; or a pharmaceutically-acceptable salt thereof.

6. Compound of Claim 5 or a pharmaceutically-acceptable salt thereof, wherein R¹ is selected from hydrido, methyl, ethyl, methoxy, ethoxy, methylthio, methylsulfinyl, methylsulfonyl, hydroxy, nitro, amino, N-methylamino, N,N-dimethylamino, acetamido, trifluoromethyl, fluoro, bromo, iodo and chloro; wherein R² is selected from hydrido, cyano, methyl, ethyl, propyl, trifluoromethyl, difluorochloromethyl, difluoromethyl, pentafluoroethyl and heptafluoropropyl; wherein R³ is selected from hydrido, methyl, ethyl, methoxy, ethoxy, methylthio, methylsulfinyl, methylsulfonyl, hydroxy, nitro, amino, N-methylamino, N,N-dimethylamino, acetamido, trifluoromethyl, bromo, iodo, fluoro and chloro; and wherein R⁴ is methyl or amino.

7. Compound of Claim 6 selected from compounds, or their pharmaceutically-acceptable salts, of the group of compounds consisting of

4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;

4-(4-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;

4-(4-bromophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;

4-(4-iodophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;

5-[4-(methylsulfonyl)phenyl]-1,4-diphenyl-3-(trifluoromethyl)-1H-pyrazole;

4-(4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;

4-(4-methylthiophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;

4-(4-methylsulfinylphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;

4-(4-hydroxyphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;

- 4-(4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 4-(4-nitrophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 5 4-(4-aminophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 4-(4-N-methylaminophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 10 4-(4-N,N-dimethylaminophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 4-(4-trifluoromethylphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 15 4-(4-acetamidophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 4-(4-[N-acetylamino]methylphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 20 1-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1-(4-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 25 1-(4-bromophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1-(4-iodophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1-(4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 30 1-(4-methylthiophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1-(4-hydroxyphenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 35 1-(4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1-(4-nitrophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;

- 1- (4-aminophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1- (4-N-methylaminophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 5 1- (4-N,N-dimethylaminophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 10 1- (4-trifluoromethylphenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1- (4-acetamidophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 15 4- (4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 4- (4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-1H-pyrazole;
- 4- (4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(methyl)-1H-pyrazole;
- 20 4- (4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(cyano)-1H-pyrazole;
- 1,4-bis(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;
- 5-[4-(methylsulfonyl)phenyl]-1,4-diphenyl-3-(difluoromethyl)-1H-pyrazole;
- 25 4-[4-(4-fluorophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-chlorophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 30 4-[4-(4-bromophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-iodophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 35 1,4-diphenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-methylphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

- 4-[4-(4-methylthiophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[4-(4-methylsulfinylphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
5 4-[4-(4-hydroxyphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[4-(4-methoxyphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[4-(4-nitrophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
10 4-[4-(4-aminophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[4-(4-N-methylaminophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
15 4-[4-(4-N,N-dimethylaminophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[4-(4-trifluoromethylphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[4-(4-acetamidophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
20 4-[4-(4-[N-acetylamino]methylphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[1-(4-fluorophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
25 4-[1-(4-chlorophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[1-(4-bromophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[1-(4-iodophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
30 4-[1-(4-methylphenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[1-(4-methylthiophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
35 4-[1-(4-hydroxyphenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
4-[1-(4-methoxyphenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

4-[1-(4-nitrophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

4-[1-(4-aminophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

5 4-[1-(4-N-methylaminophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

4-[1-(4-N,N-dimethylaminophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

10 4-[1-(4-trifluoromethylphenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

4-[1-(4-acetamidophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-1-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

15 4-[4-(4-fluorophenyl)-1-phenyl-1H-pyrazol-5-yl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-1-phenyl-3-(methyl)-1H-pyrazol-5-yl]benzenesulfonamide;

20 4-[4-(4-fluorophenyl)-1-phenyl-3-(cyano)-1H-pyrazol-5-yl]benzenesulfonamide;

4-[1,4-bis(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide; and

4-[1,4-diphenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide.

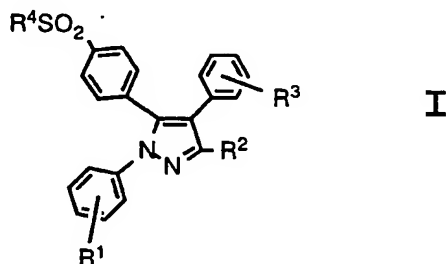
25

8. Compound of Claim 6 which is 4-(4-fluorophenyl)-5-[(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole, or a pharmaceutically-acceptable salt thereof.

30

9. A pharmaceutical composition comprising a therapeutically-effective amount of a compound and a pharmaceutically-acceptable carrier or diluent, said compound selected from a family of compounds of Formula I

5



wherein R^1 is one or more radicals independently selected from the group hydrido, halo, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, nitro, amino, N-monoalkylamino, N,N-dialkylamino, acylamino, acylaminoalkyl, haloalkyl, hydroxy and alkoxy;

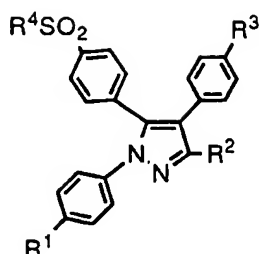
wherein R^2 is selected from hydrido, alkyl, cyano and haloalkyl;

wherein R^3 is one or more radicals independently selected from the group hydrido, halo, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, nitro, amino, N-monoalkylamino, N,N-dialkylamino, acylamino, acylaminoalkyl, haloalkyl, hydroxy and alkoxy; and

wherein R^4 is alkyl or amino; or a pharmaceutically-acceptable salt thereof.

10. A pharmaceutical composition comprising a therapeutically-effective amount of a compound and a pharmaceutically-acceptable carrier or diluent, said compound selected from a family of compounds of Formula II

50



II

wherein R^1 is selected from the group hydrido, halo, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, nitro, amino, N-monoalkylamino, N,N-dialkylamino, acylamino, acylaminoalkyl, haloalkyl, hydroxy and alkoxy; wherein R^2 is selected from hydrido, alkyl, cyano and haloalkyl;

wherein R^3 is selected from the group hydrido, halo, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, nitro, amino, N-monoalkylamino, N,N-dialkylamino, acylamino, acylaminoalkyl, haloalkyl, hydroxy and alkoxy; and

wherein R^4 is alkyl or amino; or a pharmaceutically-acceptable salt thereof.

11. The composition of Claim 10 wherein R^1 is selected from the group hydrido, halo, lower alkyl, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, nitro, amino, N-monoalkylamino, N,N-dialkylamino, acylamino, acylaminoalkyl, lower haloalkyl, hydroxy and lower alkoxy; wherein R^2 is selected from hydrido, lower alkyl, cyano and lower haloalkyl; wherein R^3 is selected from the group hydrido, halo, lower alkyl, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, nitro, amino, N-monoalkylamino, N,N-dialkylamino, acylamino, acylaminoalkyl, lower haloalkyl, hydroxy and lower alkoxy; and wherein R^4 is lower alkyl or amino; or a pharmaceutically-acceptable salt thereof.

30

12. Composition of Claim 11 wherein R^1 is selected from hydrido, methyl, ethyl, methoxy, ethoxy,

methylthio, methylsulfinyl, methylsulfonyl, hydroxy, nitro, amino, N-methylamino, N,N-dimethylamino, acetamido, trifluoromethyl, bromo, iodo, fluoro and chloro; wherein R² is selected from hydrido, methyl, ethyl, propyl, cyano, trifluoromethyl, difluorochloromethyl, difluoromethyl, pentafluoroethyl and heptafluoropropyl; wherein R³ is selected from hydrido, methyl, ethyl, methoxy, ethoxy, methylthio, methylsulfinyl, methylsulfonyl, hydroxy, nitro, amino, N-methylamino, N,N-dimethylamino, acetamido, trifluoromethyl, bromo, iodo, fluoro and chloro; and wherein R⁴ is methyl or amino; or a pharmaceutically-acceptable salt thereof.

13. Composition of Claim 12 wherein said anti-inflammatory compound is selected from compounds, and their pharmaceutically-acceptable salts, of the group of compounds consisting of

4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
4-(4-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
4-(4-bromophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
4-(4-iodophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
5-[4-(methylsulfonyl)phenyl]-1,4-diphenyl-3-(trifluoromethyl)-1H-pyrazole;
4-(4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
4-(4-methylthiophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
4-(4-methylsulfinylphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;

- 4-(4-hydroxyphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 4-(4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 5 4-(4-nitrophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 4-(4-aminophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 10 4-(4-N-methylaminophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 4-(4-N,N-dimethylaminophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 15 4-(4-trifluoromethylphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 4-(4-acetamidophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 20 4-(4-[N-acetylamino]methylphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 25 1-(4-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1-(4-bromophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1-(4-iodophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 30 1-(4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1-(4-methylthiophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 35 1-(4-hydroxyphenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1-(4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;

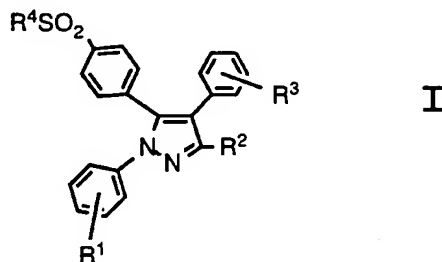
- 1-(4-nitrophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1-(4-aminophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 5 1-(4-N-methylaminophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1-(4-N,N-dimethylaminophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 10 1-(4-trifluoromethylphenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1-(4-acetamidophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 15 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-1H-pyrazole;
- 20 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(methyl)-1H-pyrazole;
- 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(cyano)-1H-pyrazole;
- 1,4-bis(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;
- 25 5-[4-(methylsulfonyl)phenyl]-1,4-diphenyl-3-(difluoromethyl)-1H-pyrazole;
- 4-[4-(4-fluorophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 30 4-[4-(4-chlorophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-bromophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-iodophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 35 1,4-diphenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

- 4-[4-(4-methylphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-methylthiophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 5 4-[4-(4-methylsulfinylphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-hydroxyphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 10 4-[4-(4-methoxyphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-nitrophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-aminophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 15 4-[4-(4-N-methylaminophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-N,N-dimethylaminophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-trifluoromethylphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 20 4-[4-(4-acetamidophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-[N-acetylamino]methylphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 25 4-[1-(4-fluorophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1-(4-chlorophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1-(4-bromophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 30 4-[1-(4-iodophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1-(4-methylphenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 35 4-[1-(4-methylthiophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1-(4-hydroxyphenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

- 4-[1-(4-methoxyphenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1-(4-nitrophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 5 4-[1-(4-aminophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1-(4-N-methylaminophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1-(4-N,N-dimethylaminophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 10 4-[1-(4-trifluoromethylphenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1-(4-acetamidophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 15 4-[4-(4-fluorophenyl)-1-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-fluorophenyl)-1-phenyl-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-fluorophenyl)-1-phenyl-3-(methyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 20 4-[4-(4-fluorophenyl)-1-phenyl-3-(cyano)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1,4-bis(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide; and
- 25 4-[1,4-diphenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide.

14. Composition of Claim 12 wherein said compound is 4-(4-fluorophenyl)-5-[(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole, or a pharmaceutically-acceptable salt thereof.
- 30

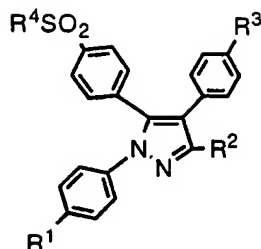
15. A method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising administering to the subject having or susceptible to such inflammation or inflammation-associated disorder, a therapeutically-effective amount of a compound of Formula I



- 10 wherein R^1 is one or more radicals independently selected from the group hydrido, halo, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, nitro, amino, N-monoalkylamino, N,N-dialkylamino, acylamino, acylaminoalkyl, haloalkyl, hydroxy and alkoxy;
- 15 wherein R^2 is selected from hydrido, alkyl, cyano and haloalkyl;
- wherein R^3 is one or more radicals independently selected from the group hydrido, halo, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, nitro, amino, N-monoalkylamino, N,N-dialkylamino, acylamino, acylaminoalkyl, haloalkyl, hydroxy and alkoxy; and
- 20 wherein R^4 is alkyl or amino; or a pharmaceutically-acceptable salt thereof.

- 25 16. A method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising administering to the subject having or susceptible to such inflammation or inflammation-associated disorder, a therapeutically-effective amount
- 30 of a compound of Formula II

57



II

wherein R^1 is selected from the group hydrido, halo, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, nitro, amino, N-monoalkylamino, N,N-dialkylamino, acylamino, acylaminoalkyl, haloalkyl, hydroxy and alkoxy;

wherein R^2 is selected from hydrido, alkyl, cyano and haloalkyl;

wherein R^3 is selected from the group hydrido, halo, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, nitro, amino, N-monoalkylamino, N,N-dialkylamino, acylamino, acylaminoalkyl, haloalkyl, hydroxy and alkoxy; and

wherein R^4 is alkyl or amino; or a pharmaceutically-acceptable salt thereof.

17. The method of Claim 16 wherein R^1 is selected from the group hydrido, halo, lower alkyl, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, nitro, amino, N-monoalkylamino, N,N-dialkylamino, acylamino, acylaminoalkyl, lower haloalkyl, hydroxy and lower alkoxy; wherein R^2 is selected from hydrido, lower alkyl, cyano and lower haloalkyl; wherein R^3 is selected from the group hydrido, halo, lower alkyl, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, nitro, amino, N-monoalkylamino, N,N-dialkylamino, acylamino, acylaminoalkyl, lower haloalkyl, hydroxy and lower alkoxy; and wherein R^4 is lower alkyl or amino; or a pharmaceutically-acceptable salt thereof.

18. The method of Claim 17 wherein R^1 is selected from hydrido, methyl, ethyl, methoxy, ethoxy, methylthio, methylsulfinyl, methylsulfonyl, hydroxy,

nitro, amino, N-methylamino, N,N-dimethylamino, acetamido, trifluoromethyl, bromo, iodo, fluoro and chloro; wherein R² is selected from hydrido, cyano, methyl, ethyl, propyl, trifluoromethyl, difluorochloromethyl, difluoromethyl, pentafluoroethyl and heptafluoropropyl; wherein R³ is selected from hydrido, methyl, ethyl, methoxy, ethoxy, methylthio, methylsulfinyl, methylsulfonyl, hydroxy, nitro, amino, N-methylamino, N,N-dimethylamino, acetamido, trifluoromethyl, iodo, bromo, fluoro and chloro; and wherein R⁴ is methyl or amino; or a pharmaceutically-acceptable salt thereof.

19. The method of Claim 18 wherein said compound is selected from compounds, and their pharmaceutically-acceptable salts, of the group of compounds consisting of

4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
4-(4-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
4-(4-bromophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
4-(4-iodophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
5-[4-(methylsulfonyl)phenyl]-1,4-diphenyl-3-(trifluoromethyl)-1H-pyrazole;
4-(4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
4-(4-methylthiophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
4-(4-methylsulfinylphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
4-(4-hydroxyphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;

- 4-(4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 4-(4-nitrophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 5 4-(4-aminophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 4-(4-N-methylaminophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 10 4-(4-N,N-dimethylaminophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 4-(4-trifluoromethylphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 15 4-(4-acetamidophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 4-(4-[N-acetylamino]methylphenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 20 1-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1-(4-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 25 1-(4-bromophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1-(4-iodophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1-(4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 30 1-(4-methylthiophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1-(4-hydroxyphenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 35 1-(4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1-(4-nitrophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;

- 1-(4-aminophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1-(4-N-methylaminophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 5 1-(4-N,N-dimethylaminophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 10 1-(4-trifluoromethylphenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 1-(4-acetamidophenyl)-5-[4-(methylsulfonyl)phenyl]-4-phenyl-3-(trifluoromethyl)-1H-pyrazole;
- 15 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(difluoromethyl)-1H-pyrazole;
- 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-1H-pyrazole;
- 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(methyl)-1H-pyrazole;
- 20 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(cyano)-1H-pyrazole;
- 1,4-bis(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;
- 5-[4-(methylsulfonyl)phenyl]-1,4-diphenyl-3-(difluoromethyl)-1H-pyrazole;
- 25 4-[4-(4-fluorophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-chlorophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 30 4-[4-(4-bromophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-iodophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 1,4-diphenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 35 4-[4-(4-methylphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

- 4-[4-(4-methylthiophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-methylsulfinylphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 5 4-[4-(4-hydroxyphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-methoxyphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-nitrophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 10 4-[4-(4-aminophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-N-methylaminophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 15 4-[4-(4-N,N-dimethylaminophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-trifluoromethylphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[4-(4-acetamidophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 20 4-[4-(4-[N-acetylamino]methylphenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1-(4-fluorophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 25 4-[1-(4-chlorophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1-(4-bromophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1-(4-iodophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 30 4-[1-(4-methylphenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1-(4-methylthiophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 35 4-[1-(4-hydroxyphenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;
- 4-[1-(4-methoxyphenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

4-[1-(4-nitrophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

4-[1-(4-aminophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

5 4-[1-(4-N-methylaminophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

4-[1-(4-N,N-dimethylaminophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

10 4-[1-(4-trifluoromethylphenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

4-[1-(4-acetamidophenyl)-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-1-phenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

15 4-[4-(4-fluorophenyl)-1-phenyl-1H-pyrazol-5-yl]benzenesulfonamide;

4-[4-(4-fluorophenyl)-1-phenyl-3-(methyl)-1H-pyrazol-5-yl]benzenesulfonamide;

20 4-[4-(4-fluorophenyl)-1-phenyl-3-(cyano)-1H-pyrazol-5-yl]benzenesulfonamide;

4-[1,4-bis(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide; and

4-[1,4-diphenyl-3-(difluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide.

25

20. The method of Claim 18 wherein said compound is 4-(4-fluorophenyl)-5-[(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-1H-pyrazole, or a pharmaceutically-acceptable salt thereof.

30

21. The method of Claim 15 for use in treatment of inflammation.

22. The method of Claim 15 for use in treatment of an inflammation-associated disorder.

35

23. The method of Claim 22 wherein the inflammation-associated disorder is arthritis.

24. The method of Claim 22 wherein the inflammation-associated disorder is pain.

5 25. The method of Claim 22 wherein the inflammation-associated disorder is fever.

INTERNATIONAL SEARCH REPORT

national Application No
PCT/US 94/12721

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D231/12 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>EP,A,0 418 845 (FUJISAWA PHARMACEUTICAL CO., LTD.) 27 March 1991 cited in the application see page 55; claim 1 see page 31; example 11.3 see page 21, line 54 - page 22, line 12 --- -/--</p>	1-25

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *I* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

28 February 1995

Date of mailing of the international search report

15. 03. 95

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (: 31-70) 340-2040, Tx. 31 651 epo nl,
Fax (: 31-70) 340-3016

Authorized officer

Fink, D

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US 94/12721

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHEMICAL ABSTRACTS, vol. 99, no. 11, 12 September 1983, Columbus, Ohio, US; abstract no. 88107t, H. BIERE ET AL. 'Nonsteroidal antiinflammatory agents, XI: Antiphlogistic pyrazole derivatives.' page 562 ;column 2 ; see abstract and Chemical Abstracts, CHEMICAL SUBSTANCES, 11th Collective Index, vol. 96-105, 1982-1986, pages 58005CS and 58053CS: RN [86768-22-1] and [86768-17-4]	1-25
Y	& ARCH. PHARM., vol.316, no.7, 1983, WEINHEIM, DE pages 608 - 616 cited in the application -----	1-25

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 94/12721

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0418845	27-03-91	AU-B- 637142	20-05-93
		AU-A- 6307290	18-04-91
		CN-A- 1050382	03-04-91
		JP-A- 3141261	17-06-91
		US-A- 5134142	28-07-92
